CASE REPORT

Successful treatment of disseminated mucormycosis in a neutropenic patient with T-cell acute lymphoblastic leukaemia

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SUMMARY

Mucormycosis is a rare angioinvasive fungal infection, more commonly seen in immunosuppressed patients, with reported mortality rates of 95% in disseminated disease. We present a case report of a patient with T-cell acute lymphoblastic leukaemia who developed disseminated infection with mucormycosis (involving the pancreas, left occipital lobe, right lower lobe of lung, appendix and right kidney) after having completed induction and consolidation chemotherapy. Growth of *Lichtheimia corymbifera* was initially isolated following a right pleural tap with fungal elements identified repeatedly on subsequent pathology specimens. Following radical surgical debridement and concurrent treatment with combination antifungal therapy, the patient survived. This case demonstrates that aggressive multisite surgical de-bulking of disseminated fungal foci, in conjunction with combination antifungal therapy and reversal of immunosuppression, can result in survival despite the grave prognosis associated with disseminated mucormycosis.

BACKGROUND

Mucormycosis is a disease caused by the filamentous fungi of the Mucorales order (class of Zygomycetes) and are not usually pathogenic to human beings unless host defences are compromised.^{1–5} The fungal sporangiospores, which exist universally in the soil and decaying organic matter, are typically inhaled or directly inoculated into disrupted skin or mucosa and can germinate in the immunocompromised host.^{1–7} Mucormycosis is associated with extensive angioinvasion, thrombosis, tissue infarction and necrosis, followed by haematogenous dissemination of the fungi.^{1–5} Dissemination occurs in up to 40% of patients with haematological malignancies⁸ and it has been reported that dissemination increases the risk of death by sevenfold.⁹

We present a case of disseminated mucormycosis infection in an immunosuppressed child following intensive chemotherapy for T-cell acute lymphoblastic leukaemia (T-ALL). This is the first known published case of a patient to survive disseminated mucormycosis with infection in five sites (right lower lobe (RLL) of lung, appendix, pancreas, left occipital lobe and right kidney) in response to prompt reversal of immunosuppression, combination antifungal therapy and aggressive multisite surgical de-bulking.

CASE PRESENTATION

An 11-year-old girl was diagnosed with T-ALL in October 2011. She had completed induction and consolidation chemotherapy without severe infective complications. Partway through receiving delayed intensification chemotherapy (vincristine, dexamethasone, doxorubicin, polyethylene glycol asparaginase, intrathecal methotrexate), she developed severe central abdominal pain (day 0). On presentation, her neutrophil count was $0.03 \times 10^9/L$ with raised C reactive protein of 270 mg/L. Lipase was normal. Urine microscopy and culture were negative. Serial CT scans (days 1 and 2) revealed consolidation and ground glass opacification of the RLL with associated pulmonary artery and vein thrombosis (figures 1 and 2), a hypodense lesion in the uncinate process of the pancreas, a lesion in the left occipital lobe (figure 3) and a lesion within the upper medial pole of the right kidney (figure 4).

Acute appendicitis was confirmed on day 5 (abdominal ultrasound) and she underwent a laparoscopic appendectomy on day 6. An MRI was performed on day 8 to investigate persistent abdominal pain radiating to the back. This demonstrated an increase in the size of the lesion in the uncinate process of the pancreas, with compression of the inferior vena cava and dilatation of the common bile duct (CBD) and the major pancreatic duct. She subsequently developed acute cholangitis and a well-defined collection behind the head of pancreas, which was highly suggestive of a ruptured distal CBD.

INVESTIGATIONS

Pleural fluid aspirate on day 4 from the right hemithorax grew *Lichtheimia corymbifera*. Histopathology of her RLL (resected on day 9) was

Figure 1 CT pulmonary angiography chest contrast: right pulmonary vein thrombosis with right lower lobe ground glass opacification and consolidative changes.

To cite: Guymer C, Khurana S, Suppiah R, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009577

Figure 2 CT pulmonary angiography chest contrast: right pulmonary artery thrombosis with opacification extending into the posterior segment of the right upper lobe.

consistent with angioinvasive mucor infection, confirming growth of *L. corymbifera*.

Histopathology of the appendix identified fungal elements consistent with the appearance of mucormycosis; however, the culture grew *Candida* and *Rhodotorula* species. This was neither thought to be clinically significant nor was it associated with the disseminated invasive fungal infection.

Subsequent histopathology specimens (from the left occipital abscess, right kidney, pancreatic abscess and biliary stent) demonstrated invasive fungal hyphae with features characteristic of mucormycosis (table 1, figures 5 and 6).

TREATMENT

Delayed intensification chemotherapy was ceased mid-cycle to avoid further myelosuppression. She responded well with her neutrophil count increasing to $1.70 \times 10^9/\text{L}$ by day 6.

Given her excellent premorbid functional status and prompt recovery of the neutrophil count, a decision was made to treat this disseminated mucormycosis aggressively—utilising combination antifungal therapy and targeted surgical debridement of fungal foci.

Antifungal therapy with intravenous liposomal amphotericin B (L-AMB) was increased from a dose of 5 to 10 mg/kg/day.

Figure 3 CT head contrast: ring-enhancing lesion left occipital lobe ($1.8 \times 1.2 \times 2.4$ cm).

Figure 4 CT abdomen contrast: hypodense lesion in the uncinate process of the pancreas ($5.1 \times 4.2 \times 4.1$ cm), lesion within the upper medial pole of the right kidney (1.0×0.9 cm).

Caspofungin (70 mg/m^2 loading dose then $50 \text{ mg/m}^2/\text{day}$) was also started for its synergistic effect with L-AMB.

Caspofungin was ceased on day 68 and L-AMB therapy was reduced to a daily regimen of 5 mg/kg/day on day 82. Oral posaconazole was also introduced at this time; but was discontinued after 3 months due to failure to achieve satisfactory therapeutic levels. Absorption and resultant bioavailability of posaconazole is best achieved when taken with a high fat meal.¹⁰ This has not been possible due to erratic oral nutritional intake secondary to on-going recurrent abdominal pain.

Surgical management has involved: (1) right lower lobectomy, (2) craniotomy for drainage of her left occipital abscess, (3) left superior turbinectomy and sphenoidotomy, (4) right nephrectomy (attempted laparoscopic partial nephrectomy converted to open total nephrectomy), (5) percutaneous drainage of her pancreatic abscess plus multiple endoscopic retrograde cholangiopancreatography with sphincterotomy and pancreatobiliary stenting, (6) emergency stenting of (presumed mycotic) superior mesenteric artery (SMA) aneurysm presenting with sudden onset of haemodynamic instability and frank haemorrhage through her peripancreatic drain (day 34) and (7) laparotomy, cholecystectomy and hepaticoduodenostomy for persistent biliary leakage from the disrupted distal CBD (day 46).

OUTCOME AND FOLLOW-UP

The patient is currently in remission with no signs of mucormycosis. Her most significant on-going problem is recurrent abdominal pain that is unexplained. The SMA stent has been proven to be patent on serial Doppler sonographic scanning. Multiple replacements of the pancreatic stent have made no difference to her symptoms. A pancreatic secretin stimulation test demonstrated normal pancreatic function and did not stimulate her abdominal pain. At present her abdominal pain is being managed by the chronic pain service.

DISCUSSION

The true incidence of mucormycosis is unknown, as most epidemiological studies are retrospective and therefore limited.^{1 11} Patients known to be at risk of developing mucormycosis include those with haematological malignancies, haematopoietic stem cell transplant recipients, solid organ malignancies, solid organ transplantation recipients, graft versus host disease, autoimmune disorders, diabetes mellitus, major trauma, neonatal prematurity and users of illicit drugs.^{1 2 4 5 7} Mucormycosis infection has been reported with increasing frequency in immunocompromised patients with haematological malignancies (8/100 000 in

Table 1 Summary of operations, histopathology and microscopy/culture findings

Operation	Cytology and histopathology	Microscopy and culture
Right pleural tap	No malignant cells	+++ fungal elements identified with growth of <i>Lichtheimia corymbifera</i>
Laparoscopic appendectomy	Acute appendicitis, fungal elements identified	Fungal elements identified consist with appearance of mucormycosis. Growth of <i>Candida</i> sp. non-albicans and growth of <i>Rhodotorula</i> sp. No fungal growth in peritoneal fluid
Right thoracotomy and right lower lobectomy	Septic thromboembolic disease with numerous fungal hyphae within vessels, haemorrhagic infarction of the lung with suppuration and abscess formation	+++ fungal elements identified with growth of <i>L. corymbifera</i> (sensitive to Amphotericin B)
Drainage of pancreatic abscess	Fungal hyphae identified	No fungal elements detected on direct microscopy. No fungal nor bacterial growth.
Craniotomy for drainage of left occipital abscess	Fungal organisms were observed to have the same morphology as seen in the lung and the appendix. Evidence of granulomatous inflammation and abscess formation	+++ fungal elements identified, with negative culture results
Superior turbinectomy, sphenoidotomy	No fungal hyphae present	No fungal elements detected on direct microscopy. Negative culture results
Right open nephrectomy	Two foci of renal infarction with abscess and granulomatous inflammation incorporating numerous fungal hyphae similar to those seen in previous samples	+++ fungal elements identified. Negative culture results
Laparotomy, cholecystectomy, biliary stent removed, hepaticoduodenostomy	Gallbladder: mild inflammatory changes, no evidence of fungal organisms	Gallbladder: no fungal elements detected and no fungal growth. Biliary stent: + fungal elements: no fungal growth

1989–1993 to 17/100 000 in 1994–1998),¹ possibly due to more aggressive treatments resulting in more severe and prolonged postchemotherapeutic neutropenia.^{1 2 5 8 11–13} The diagnosis of mucormycosis is often made at autopsy, representing 8.3–13% of all fungal infections in high-risk patients and has an incidence of 0.4–0.9% on patients with haematological malignancies.^{1 3 4 11} The outcome in disseminated infection is dismal, with up to 95% of all patients not surviving the infection irrespective of the antifungal treatment administered.^{1 2 7 12}

Early diagnosis is critical to early therapeutic intervention to prevent progressive angioinvasion and dissemination, reduce the extent of surgical resection and improve outcome and survival.^{1 2 4–6 11 14} Definitive diagnosis must be established by biopsy and cultures.^{4 6} Cultures of fresh tissue more frequently yield a positive result than body fluids or necrotic tissue.^{2 5} Histology characteristically demonstrates wide non-septate hyphae that branch at right angles and look empty when stained with H&E.^{2 7 11} CT findings may be suggestive of fungal infection, yet are often non-specific and cannot be distinguished from other infective causes.^{4 14}

Treating a patient's underlying medical condition and resolution of chemotherapy-induced neutropenia are also essential to therapy.^{5 6 8 11 14} In vitro studies have demonstrated synergistic activity of neutrophils and L-AMB against Mucorales.¹⁴ In our patient's case, prompt recovery of her neutropenia early in the course of her disease appeared to play a critical role for her survival. Granulocyte transfusions can offer support for persistently neutropenic patients until recovery from neutropenia.¹⁴ Granulocyte colony-stimulating factor or interferon- γ may help to further augment the host response and antifungal effect in non-neutropenic patients with refractory disease.¹⁴

Several in vitro studies have proved excellent activity of amphotericin B against Mucorales and is thus recommended as first-line therapy.^{6 8 12 13} The lipid formulation of amphotericin B is preferred as it is associated with less nephrotoxicity and can therefore be administered at higher doses for longer periods and is associated with higher cure rates in central nervous system (CNS) mucormycosis.^{6 14 15} The optimal daily dose and length of treatment of amphotericin B are undefined and it is not clear whether higher doses lead to improved outcomes.^{6 13 14}

Figure 5 Silver-stain right lower lung: numerous fungal hyphae within vessels.

Figure 6 Left occiput: granulomatous inflammation and abscess formation with numerous fungal hyphae.

Current guidelines based on pharmacokinetic data recommend dosing of L-AMB at 5 mg/kg/day, which can be increased to 10 mg/kg/day in patients with CNS involvement.¹⁴

There is limited evidence for combination antifungal therapy of L-AMB with caspofungin (an echinocandin). Its synergistic activity has been demonstrated in murine models with disseminated mucormycosis, when compared with monotherapy or placebo.^{6 14 16} Superior outcomes have also been suggested in retrospective clinical studies with combination caspofungin and L-AMB therapy for rhino-orbital-cerebral mucormycosis.¹⁴ The new extended-spectrum triazole antifungal agent, posaconazole, has shown to have significant activity against mucormycosis and may have the potential for clinical development in the treatment of mucormycosis.^{5 7 9 15} Overall success rates of 60–70% (complete plus partial response) have been reported from retrospective case series when used as salvage therapy in combination with amphotericin B for mucormycosis.^{9 14} Guidelines from the Third European Conference on Infections in Leukaemia (ECIL 3) recommend that L-AMB in conjunction with posaconazole is reserved as second-line therapy for patients with mucormycosis who are refractory or intolerant to L-AMB (level B II evidence).⁶

Surgery, independent of concurrent L-AMB therapy, has been demonstrated to improve survival.^{6 8 13} The most comprehensive systematic review by ECIL 3, examining 929 published cases between 1885 and 2005, found that patients treated with antifungal therapy and surgery had significantly improved mortality rates than those treated with L-AMB alone (70% vs 57%, respectively).⁶ This agrees with the findings of a review of 255 cases of pulmonary mucormycosis published by Tedder *et al*² who reported that the mortality rate was significantly lower for patients who underwent surgery than for those who received medical treatment only (9.4% vs 50%, $p=0.01$).¹¹ This is further supported by a systematic review by Zaoutis *et al*⁹ who found that antifungal therapy combined with surgery significantly reduced the risk of death by 84%. It is also noteworthy that those patients treated aggressively with L-AMB combined with surgical debridement were able to tolerate further intensive chemotherapies without relapse of infection.¹¹ ECIL 3 recommends the timely maximal debridement of infected tissue, par-

ticularly in rhino-cerebral, skin and soft tissue disease (level A II evidence), to reduce the fungal load and prevent extension, angioinvasion and dissemination of mucormycosis.⁶

In conclusion, we believe the factors contributing to the effective treatment of disseminated mucormycosis and survival of our patient were: (1) a high index of clinical suspicion of disseminated fungal infection, therefore prompting vigorous microbiological isolation and diagnosis; (2) early intensive combination antifungal therapy with high-dose parenteral L-AMB and caspofungin; (3) radical surgical debridement of fungal foci and (4) prompt resolution of her neutropenia following the suspension of myelosuppressive agents. This agrees with the consensus upon review of the literature.^{6 13}

Acknowledgements We would like to thank the following clinicians for their contribution to this patient's care: Mr Christopher Kirby, Dr Cindy Molloy, Mr Ian Wong, Mr John Chen, Mr Craig Jurisevic, Dr Mike Wilks.

Contributors CG wrote the case report, collated the clinical data, undertook the literature search and is the guarantor for the case. SK, RS and CC contributed to the interpretation of clinical data, critical review of drafts and final approval of the version to be published. IH suggested writing the case for publication, assisted in the collation and interpretation of clinical data, and critical review of drafts.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Mucormycosis is a rare fungal infection predominantly seen in immunocompromised patients with high mortality rates of up to 95% in disseminated disease.
- Improved prognosis can be achieved with early diagnosis based on a high clinical index of suspicion and microbiological isolation of mucormycosis infection, recovery of underlying immunosuppression and prompt intensive treatment.
- Early intensive treatment with combination antifungal therapy with high-dose parenteral liposomal amphotericin B and caspofungin, aggressive surgical resection of fungal foci and reversal of immunosuppression are imperative to improve chances of survival.

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